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Unusual Reactions Between Aromatic Carbon Supernucleophiles and 1,2-Diazabuta-1,3-dienes: Useful Routes to New Pyrazolone and Cinnoline Derivatives

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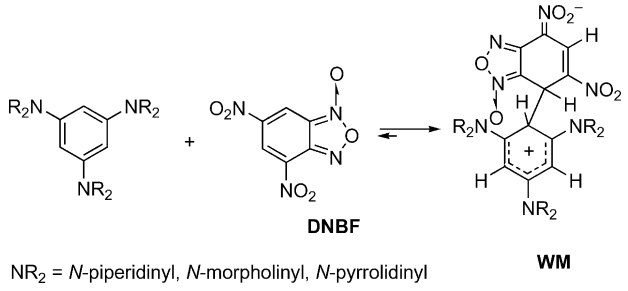
Keywords: Aromatic substitution / Cyclization / Heterocycles / Michael additions

Reactions between 1,3,5-tris(dialkylamino)benzenes and 1,2-diazabuta-1,3-dienes produce semicarbazone derivatives through attack of the supernucleophile aromatic carbon atom at the terminal carbon atom of the heterodiene reagent. The strong activation of the aromatic ring due to the presence of the three amino groups in a symmetrical relationship promotes electrophilic aromatic substitution by the neutral carbon atom of the electrophile. The resulting semicarbazones, in methanol in the presence of sodium methoxide, mainly afford pyrazolone derivatives, whereas in THF in the presence of sodium methoxide an unusual cyclization reaction produces cinnoline derivatives as the major products. Both cyclization reaction mechanisms are discussed.

Introduction

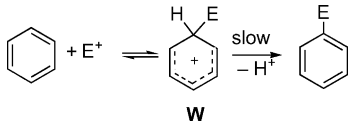
1,3,5-Tris(dialkylamino)benzene derivatives are strongly activated neutral carbon nucleophiles able to display some reactivity aspects toward electrophilic substrates featuring a greater or lesser degree of activation. These very interesting electron-rich benzenes were first synthesized in 1967[1a] and were extensively studied[1] by Effenberger et al. Their supernucleophilic character permits reactions to be performed under particularly mild conditions, and makes them suitable for mechanistic investigations. Recently, we isolated σ-complexes (the so-called Wheland intermediates, **W**) from electrophilic aromatic reactions between these nucleophiles and diazonium salts.[2] Furthermore, reactions between 1,3,5-tris(dialkylamino)benzene derivatives and a more electrophilic reagent – namely 1,4-dinitrobenzofuroxan (**DNBF**) – permitted us to obtain the first evidence of a carbon–carbon Wheland–Meisenheimer complex (**WM**, Scheme 1), which was studied by NMR spectroscopy.[3a]

This observation is consistent with the strong electrophilic power of **DNBF**, as quantitatively indicated by Terrier[4] on the Mayr[5] electrophilicity scale. In the case of reactions between **DNBF** and 2-aminothiazole derivatives we also collected evidence of the presence of **WM** intermediates arising from the attack of the electrophilic reagent at the 5-positions in the thiazole rings.[3b,3c]



Scheme 1. First examples of Wheland–Meisenheimer carbon–carbon adducts.

The capability to form moderately stable Wheland intermediates depends both on the activation of the reagents and on experimental conditions that slow the proton elimination in the rearomatization process,[2b,2c] as shown in Scheme 2.



Scheme 2.

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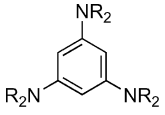
Especially when electron-withdrawing groups are present on the terminal carbon and/or nitrogen atoms, heterodiene systems containing diaza groups are well-known electrophiles, able to undergo nucleophilic attack to yield Michael-like adducts. These 1,4-additions to 1,2-diazabuta-1,3-dienes (**DBD**s) with formation of new carbon–carbon or carbon–heteroatom bonds have been carried out with a wide number of carbon (as activated methylene and methyne compounds), oxygen, nitrogen, sulfur, selenium and phosphorus nucleophiles.[6,7] Previously, it had been reported[8] that reactions between 1,2-diazabuta-1,3-dienes and amines take place by the classical nitrogen attack at the terminal carbon atom of the heterodiene reagent to afford α-aminohydrazones, which represent interesting intermediates from which to obtain many heterocyclic systems.

On the basis of these findings, and in view of the nucleophilic power at the aromatic carbon atoms exhibited by 1,3,5-tris(dialkylamino)benzene derivatives, we decided to investigate the behaviour of these neutral carbon nucleophiles in Michael-type additions with **DBD**s under mild neutral conditions.

Here we report that the addition reactions between the 1,3,5-tris(dialkylamino)benzenes **1** and **2** and several **DBD**s take place easily, affording the addition products in high yields. Under basic conditions these addition products undergo cyclization, which can switch toward preferential formation either of pyrazolone derivatives or of cinnoline derivatives, depending on the solvent used.



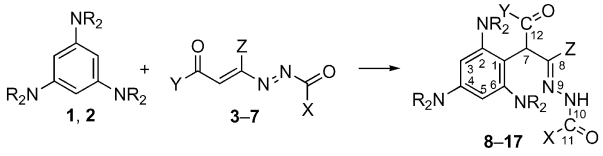
R_2N = piperidinyl (**1**); morpholinyl (**2**)

Results and Discussion

A) Reactions Between 1,3,5-Tris(dialkylamino)benzenes and 1,2-Diazabuta-1,3-dienes

Usually, **DBD**s react with nucleophilic reagents, and the reactions are promoted by the presence of bases. Base catalysis may be necessary to activate the nucleophilic centres, as in the case of β-dicarbonyl derivatives. Often, the presence of a base makes it difficult to isolate Michael-type adducts, because the subsequent cyclization to heterocyclic systems may take place rapidly. Our previous findings suggested to us that 1,3,5-triaminobenzenes (**TAB**s) might be reagents so strongly activated as to allow attack at the neutral electrophilic terminal carbon atom of the heterodiene moiety of a **DBD**, and this prompted us to explore that possibility.

Michael-like adducts **8**–**17** were obtained by addition, at room temperature, of equimolar amounts of **TAB**s (**1** or **2**) in chloroform to **DBD**s (**3**–**7**) in the same solvent, as shown in Scheme 3. The disappearance of the typical red colour of the starting **DBD**s revealed the completion of the reactions.



1, **2** + **3**–**7** → **8**–**17**

R_2N = piperidinyl (**1**)
R_2N = morpholinyl (**2**)

Y = OEt, X = NH_2, Z = Me, **3**
Y = OMe, X = NH_2, Z = Me, **4**
Y = OMe, X = NH_2, Z = Et, **5**
Y = NMe_2, X = NH_2, Z = Me, **6**
Y = NMe_2, X = NHPh, Z = Me, **7**

Comp.	Y	X	Z	Comp.
8	OEt	NH_2,	Me	**13**
9	OMe	NH_2,	Me	**14**
10	OMe	NH_2,	Et	**15**
11	NMe_2	NH_2,	Me	**16**
12	NMe_2	NHPh,	Me	**17**
NR_2 = piperidinyl		NR_2 = morpholinyl		

Scheme 3. Michael-like addition reaction between **TAB**s and **DBD**s.

Table 1 reports the yields of semicarbazones **8**–**17**, the physical properties and NMR spectroscopic data of which, reported in the Experimental Section, agree with the structures shown in Scheme 3. It has to be noted that, in the case of reactions of **DBD**s with **1**, the ^{1}H NMR spectra of the crude reaction mixtures showed complete conversion after about 1 h, whereas the conversion of the morpholinyl derivative **2** required longer reaction times (from 2 to 8 h) and in some cases did not go to completion. The piperidinyl derivative **1** is more reactive than the morpholinyl derivative **2**, as would be expected on the basis of the electron-withdrawing character of the morpholine oxygen atom as indi-

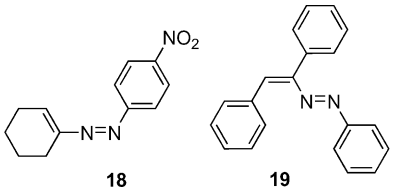
Table 1. Semicarbazones obtained from **TAB**s **1** and **2** and **DBD**s **3**–**7**.

R_2N	Y	X	Z	Conversion (product ratio)[a]	Product[b] (yield%)
Piperidinyl	OEt	NH_2	Me	100% (80:20)	**8** (77)[c]
Piperidinyl	OMe	NH_2	Me	100% (80:20)	**9** (70)[c]
Piperidinyl	OMe	NH_2	Et	100% (75:25)	**10** (74)[c]
Piperidinyl	NMe_2	NH_2	Me	100% (100:0)	**11** (96)[c]
Piperidinyl	NMe_2	NHPh	Me	100% (100:0)	**12** (95)[d]
Morpholinyl	OEt	NH_2	Me	82% (83:17)	**13** (55)[d]
Morpholinyl	OMe	NH_2	Me	100% (85:15)	**14** (83)[d]
Morpholinyl	OMe	NH_2	Et	100% (80:20)	**15** (76)[d]
Morpholinyl	NMe_2	NH_2	Me	100% (100:0)	**16** (93)[d]
Morpholinyl	NMe_2	NHPh	Me	70% (100:0)	**17** (65)[d]

[a] Relative % ratio of products, calculated from the ^{1}H NMR spectrum of the crude reaction mixture and referenced to the main compound (**8**–**17**) with respect to a second product, as discussed in the text. [b] Product isolated by precipitation. [c] Yield of weighed product precipitated from acetonitrile reaction mixture (second procedure, see Exp. Sect.). [d] Yield of weighed product obtained from the first procedure (see Exp. Sect.).

cated by, for instance, the pK_a difference [pK_a(morpholine) = 16.6, pK_a(piperidine) = 18.9].[9] In some cases ^{1}H NMR spectra of the crude reaction mixtures showed the presence of signals for compounds **8**–**17** together with those of similar products (see later), in about 15–25% relative ratio. Compounds **8**–**17** were isolated in high purity (>98%) by precipitation from acetonitrile (see Exp. Sect.).

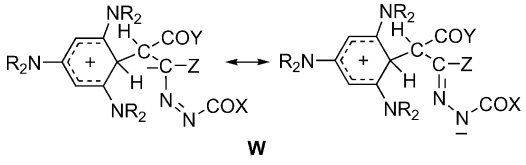
When reactions between **1** or **2** and 1-(cyclohex-1-en-1-yl)-2-(4-nitrophenyl)diazene (**18**) were attempted, no reaction products were detected, and after 72 h the decomposition of **18** became relevant. This was presumably the result of the absence of electron-withdrawing groups on the terminal carbon and/or nitrogen atoms of the heterodiene system.



18 **19**

The lack of any reaction of **18** may be explained by bearing in mind that the electron-withdrawing electronic effects of COOR or $CONMe_2$ groups enhance the electrophilic power of the heterodiene terminal carbon atoms of **DBD**s **3**–**7**. This supposition is also confirmed by the absence of conversion in the reaction between **1** and **19**.

The success achieved in obtaining stable Michael-type adducts under neutral conditions prompted us to perform the reaction in an NMR tube. Indeed, in view of our previous work,[2,3] evidence of Wheland intermediates (**W**, Scheme 4) might be expected at low temperatures.

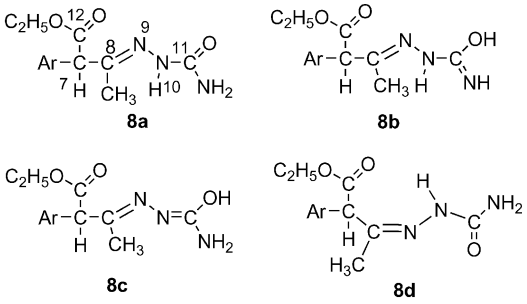


Scheme 4.

The reactions between compounds **1** or **2** and **DBD 3** were carried out directly in NMR tubes in different solvents ($CDCl_3$, CD_2Cl_2, CD_3CN) and at different temperatures (from –70 to +25 °C), but no evidence of the presence of possible **W** complex-like intermediates in detectable amounts was obtained. The only recorded signals were those associated with the starting materials and with the final semicarbazone derivatives, together (in cases of long reaction times) with small amounts of isomeric forms and of heterocyclic derivatives (see following sections).

Isomerism of Semicarbazones 8–17

^{1}H NMR spectroscopic data, recorded in $CDCl_3$, for all semicarbazones **8**–**17** show very close chemical shift values (see Exp. Sect.). Consequently, it is reasonable to suppose that **8**–**17** have a common form. In particular, singlets at δ = 6.6–6.7 ppm are clearly attributable to the two equivalent protons 3-H and 5-H of the aromatic rings (Scheme 5). The singlets at δ = 5.2–5.4 ppm are in the region relating to protons in benzylic positions and adjacent to electron-withdrawing groups, as would be expected for 7-H. N–H protons exchanged quickly (H/D) on addition of D_2O, while protons bonded to C-7 exchanged slowly (in about 12 h), as would be expected for protons bonded in positions α to COOR groups. In the cases of adducts **11**, **12**, **16** and **17**, bearing amido groups instead of ester groups, 7-H did not exchange.



Ar = 2,4,6-tripiperidinobenzene or 2,4,6-trimorpholinobenzene

Scheme 5. Isomeric forms for compound **8**.

It is worthy of attention that ^{1}H NMR spectra of adducts **8**–**10** and **13**–**15** recorded immediately after their dissolution in $CDCl_3$ slowly change with time. Figure 1a and b show ^{1}H NMR spectra of compound **8** (chosen as an exam-

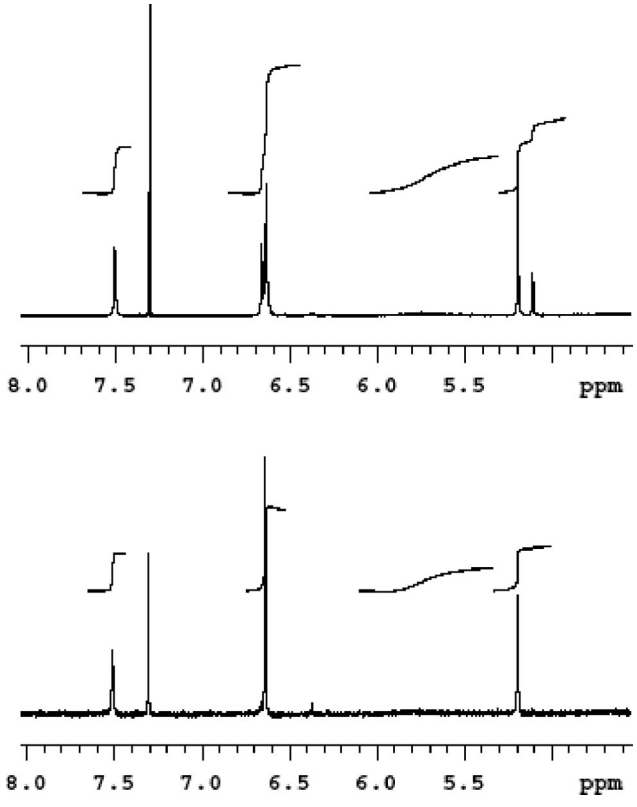


Figure 1. ^{1}H NMR spectra (selected window) of compound **8**. Bottom: spectrum recorded immediately after dissolution in $CDCl_3$. Top: spectrum recorded after 2 d.

ple for discussion) recorded immediately after dissolution in $CDCl_3$, and after about 2 d, respectively.

New signals at δ = 5.1, 6.7 and 2.4 (CH_3) ppm, similar to those of the starting compound, appeared. The gHSQC spectrum showed that the signal at δ = 5.11 ppm belongs to a proton bonded to C-7.

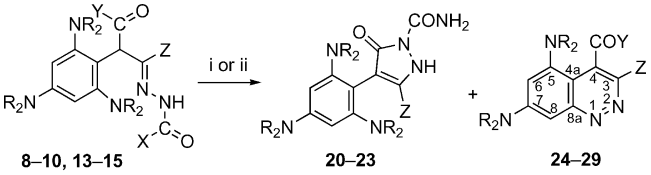
Prototropism of **8a** can generate **8b** and **8c** (Scheme 5). Among all the tautomeric forms, our data clearly indicate **8b** and **8c** as the most populated tautomers. The greater extent of electronic conjugation in **8c** with respect to **8b** favours **8c** over **8b**. In addition, the presence, in the ^1H NMR spectrum (see Exp. Sect.) of two distinct signals that exchange with D_2O in a 2:1 relative ratio also supports this conclusion.

After 2 d in $CDCl_3$, the relative amount of the new compound has reached 15–25% with respect to the starting semicarbazone. Attempts to modify the relative ratio of signals associated with these isomeric forms by performing several VT NMR experiments in CD_3CN at temperatures varying from –30 to +75 °C did not produce evidence of modifications of the relative amounts of these isomers. Other possible attributions of the new signals might also relate to *syn*/*anti* isomerism. Although the lack of observation of any effect of variation of the temperature reduces this possibility, the observation of a positive NOE effect supports the possibility that the new signals may be associated with a *syn* form of compound **8**, as represented by **8d**. In all cases, the ^1H NMR spectrum in [D_6]DMSO shows the presence of one product only.

Michael adducts **11**, **12**, **16** and **17** – bearing –CON(CH_3)$_2$ groups, with their feeble electron-withdrawing effects – did not show evidence of new isomeric forms.

B) Cyclization Reactions of Semicarbazones 8–17

In the presence of sodium methoxide, compounds **8**–**10** and **13**–**15** underwent cyclizations to produce pyrazolone derivatives **20**–**23** and cinnoline derivatives **24**–**29** in different relative ratios depending on the solvent used (Scheme 6). The pairs of reaction products were easily separable by column chromatography and fully characterizable, and their spectroscopic data agree with the structures shown here. It is noteworthy that the formation of pyrazolones under basic conditions had already been observed with similar adducts,[6a–6c] whereas the formation of cinnoline derivatives is a new and completely unexpected result, because in this latter case the ring-closure implies an intramolecular nucleophilic substitution on the aromatic ring with release of a morpholinyl (or piperidinyl) group. Clearly, the absolute and relative yields of pyrazolones and cinnolines are structure- and conditions-dependent.



Comp.	Y	X	Z	Comp.
8	OEt	NH_2,	Me	**13**
9	OMe	NH_2,	Me	**14**
10	OMe	NH_2,	Et	**15**
NR_2: piperidinyl		NR_2: morpholinyl		

Comp.	Y	Z	Comp.
20		Me	**22**
21		Et	**23**
24	OEt	Me	**27**
25	OMe	Me	**28**
26	OMe	Et	**29**
NR_2: piperidinyl		NR_2: morpholinyl	

i : CH_3ONa/THF: **20**–**23** (7–50%), **24**–**29** (93–50%)

ii: CH_3ONa/CH_3OH: **20**–**23** (95–50%), **24**–**29** (5–50%)

Scheme 6. Cyclization reactions of the adducts **8**–**10** and **13**–**15**.

1. Formation of Pyrazolones as Major Products

In methanol with 1 equiv. of sodium methoxide, semicarbazones **8**–**10** and **13**–**15** cyclized to give pyrazolones **20**–**23** (see Table 2). Piperidinyl (**8**–**10**) and morpholinyl (**15**) derivatives give pyrazolones **20**, **21** and **23** as major products, whereaas morpholinyl derivative **22** was obtained in equimolar amounts with respect to the cinnoline derivatives **27** and **28**. (Obviously, the same pyrazolone **20** was obtained from **8** and **9**, whereas **22** was also obtained from both **13** and **14**.)

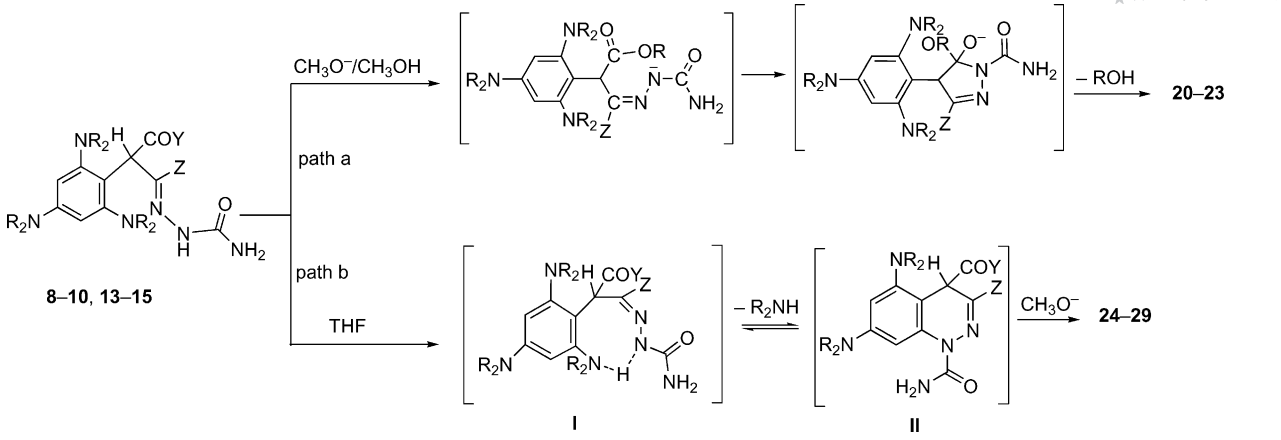
The presence of the two different heterocycle systems can be clearly observed in the ^1H NMR spectra of the crude reaction mixtures, each of which shows two signals, of relative intensity 1:1, in the spectral region for aromatic C–H (δ = 7.3–7.6 ppm in $CDCl_3$), attributable to the cinnoline derivative, and one singlet at δ = 6.41–6.46 ppm, corresponding to the hydrogen atoms of the aromatic ring of the pyrazolone derivative.

The importance of the presence of the base in the cyclization reactions affording pyrazolone derivatives may be explained in terms of the formation of a powerfully charged nitrogen nucleophilic centre and subsequent ring closure

Table 2. Pyrazolones obtained from semicarbazones by cyclization in methanol in the presence of sodium methoxide.

Starting compd.	Y	Z	Conv.[a]	Pyrazolone vs. cinnoline (relative % ratio)[a]	Pyrazolone (yield %)[b]
8	OEt	Me	100%	**20** (73) **24** (27)	**20** (70)
9	OMe	Me	100%	**20** (80) **25** (20)	**20** (77)
10	OMe	Et	100%	**21** (95) **26** (5)	**21** (92)
13	OEt	Me	95%	**22** (50) **27** (50)	**22** (40)[c]
14	OMe	Me	50%	**22** (50) **28** (50)	**22** (25)[c]
15	OMe	Et	95%	**23** (62) **29** (38)	**23** (55)[c]

[a] Calculated from the ^1H NMR spectrum of the crude reaction mixture. [b] Yield of pure product weighed after chromatographic separation. [c] Low yield due to incomplete conversion caused by poor solubility of starting materials.



Scheme 7.

through acylic nucleophilic substitution (Scheme 7, path a).

However, small amounts of pyrazolones are also formed simply on chromatographic columns (silica gel, elution with methanol) without base catalysis, and also in THF, in a very slow and incomplete process. This occurrence can be easily explained by considering that some basic centres, able to favour proton departure and thus promoting the ring-closure reaction, are present in the semicarbazone derivatives. Obviously, the addition of a strong base, such as sodium methoxide, strongly favours this reaction.

In Scheme 7, the ring-closure of the derivatives **8**–**10** and **13**–**15** to pyrazolone derivatives may be conceived as occurring out of the plane of the benzene ring.

Compounds **11**, **12**, **16** and **17** (Y = NMe_2) are not prone to cyclization to yield pyrazolones, probably because the carbonyl carbon atoms of their amido groups are less activated toward nucleophilic attack than ester carbonyl groups. In addition, the protons α to the amido $CO(NMe)_2$ groups of compounds **11**, **12**, **16** and **17** are less acidic than those α to the ester groups in the adducts that gave pyrazolone derivatives **20**–**23**.

2. Formation of Cinnolines as Major Products

In vigorously stirred THF with 2 equiv. of sodium methoxide, pyrazolone and cinnoline derivatives are obtained from semicarbazones **8**–**10** and **13**–**15** in relative ratios different from those obtained in methanol (see Table 3). The change of the solvent from methanol to THF permits the reaction pathway to be driven preferentially toward the formation of cinnoline derivatives (in the case of the starting compound **9**, almost exclusively).

Some reactions were also carried out under different experimental conditions. In THF, compound **8** showed similar behaviour on addition of aq. NaOH (0.1 M, 2 equiv.), whereas a substitution of CH_3ONa with DABCO gave rise to low levels of conversion and only traces of cyclization products. In THF in the absence of base, the cyclization of **15** was very slow (50% of conversion in 11 d) and produced only the pyrazolone derivative. The reaction between compound **10** and CH_3ONa was carried out in CD_3CN, and its behaviour was monitored by ^1H NMR spectroscopy, showing the formation of the cyclization products **21** and **26** in about 4:6 relative ratio. These findings clearly indicate that the two ring-closure reactions giving pyrazolones or cinnolines are in competition and that the preferential formation of a five- or a six-membered ring mainly depends on the solvent used. In more strongly associating solvents, such as THF and CH_3CN, the formation of cinnolines predominates (Scheme 7, path b).

The unexpected formation of cinnoline derivatives is also an interesting finding from the synthetic point of view, as these heterocycles find application in the agrochemical, biological and pharmaceutical fields.[10] Some derivatives exhibit anti-inflammatory and antibiotic activity. Sometimes they are synthesized from *o*-aminophenylethylene or *o*-aminoacetophenones,[11] but the main routes are the cyclization of *ortho*-substituted arylhydrazones or the diazotization of *o*-substituted anilines.[12–14] The cyclization of hydrazones is achieved through Friedel–Crafts-type reactions.[14] In view

Table 3. Cinnolines obtained from semicarbazones by cyclization in THF in the presence of sodium methoxide.

Starting compd.	Y	Z	Conv.[a]	Cinnoline vs. pyrazolone (relative % ratio)[a]	Cinnoline (yield %)[b]
8	OEt	Me	100%	**24** (75) **20** (25)	**24** (72)
9	OMe	Me	95%	**25** (93) **20** (7)	**25** (90)
10	OMe	Et	100%	**26** (55) **21** (45)	**26** (46)
13	OEt	Me	67%	**27** (85) **22** (15)	**27** (55)[c]
14	OMe	Me	100%	**28** (58) **22** (42)	**28** (41)
15	OMe	Et	85%	**29** (69) **23** (31)	**29** (46)[c]

[a] Calculated from the ^1H NMR spectrum of the crude reaction mixture. [b] Yield of pure product weighed after chromatographic separation. [c] Low yield due to incomplete conversion caused by poor solubility of starting materials.

of the importance of these compounds, we emphasize that the current reaction represents a new route to cinnoline derivatives under mild experimental conditions and in good to satisfactory yields. In addition, the presence of the ester functionalities in the 4-positions of the cinnoline derivatives **24**–**29** makes it possible to synthesize other derivatives.

Usually, the synthetic approach involving formation of the cinnoline N-1–C-8a bond involves cyclization of *o*-halogeno-α-hydrazonoacetophenones or related substrates[15] in which the formation of the six-membered ring proceeds in an S_NAr fashion with displacement of the halide ion.[15] It is noteworthy that the reaction pathway for the formation of cinnolines reported here involves a secondary amine (piperidine or morpholine) as a leaving group. The replacement of amines in nucleophilic aromatic substitution reactions has scarcely been investigated, though it has been reported to occur[16] on aromatic substrates bearing electron-withdrawing groups (e.g., nitro groups). In the reaction reported here, strongly electron-donating groups are bonded to the aromatic ring, so this reaction appears to be highly unusual. However, the incipient charge separation, and the closeness of both entering and leaving groups (as depicted in **I**), facilitate six-membered ring-closure. Obviously, the driving force for the new ring-formation is the final aromatization step. In fact, the ring-closure and the departure of the amino group is possible if the proton bonded to the ureidic nitrogen atom α to the carbonyl amido group is shifted onto the aromatic amino group as shown in the first equilibrium of Scheme 7, path b, thus facilitating the subsequent loss of the neutral amine from intermediate **I**. After the ring-closure, the sodium methoxide promotes the aromatization of the heterocyclic ring.

As with the cyclization to pyrazolones, the formation of cinnoline derivatives does not occur with Michael-type adducts bearing $CON(CH_3)_2$ groups rather than COOR groups. This may be explained by considering that the formation of a negative charge on the ureidic nitrogen atom capable of causing the aromatic nucleophilic substitution on the aromatic ring can be achieved through different pathways involving internal proton shifts. In this context, the higher acidities of the 7-H protons of compounds **8**–**10** and **13**–**15** with respect to those of adducts **11**, **12**, **16** and **17** (see previous section on tautomerism) can play an important role.

Finally, we would like to focus attention on a further particularity of the compounds synthesized in this work. It is predictable that the presence of bulky groups, such as piperidinyl or morpholinyl substituents, in all the compounds synthesized here should make these molecules quite rigid. This hypothesis is confirmed by the fact that ^1H NMR spectra of compounds **8**, **13**, **24** and **27** each present two signals, one for each methylene hydrogen atom of the ethoxycarbonyl group. This evidence clearly indicates non-equivalence of the two methylene hydrogen atoms, probably due to a rotational constraint of the ester group caused by the proximity (*peri* position) of the piperidinyl (or morpholinyl) group. This non-equivalence is also evident for the methylene signals of the piperidinyl (or morpholinyl) substituents adjacent to the ring-fused carbon atoms of all the cinnolines synthesized (and of many other compounds reported here), which appear as broad signals, both in ^1H and in ^{13}C NMR spectra (see the Supporting Information). This observation prompted us to perform dynamic ^1H NMR experiments at different temperatures on cinnoline derivative **27**, chosen as an example. Increasing of the temperature of a [D_6]DMSO solution of compound **27** from 25 to 115 °C caused, at first, the coalescence of the two methylene broad signals, and then their gradual sharpening to show a quartet centred at $\delta = 4.50$ ppm, with a coupling constant of 7.0 Hz with the adjacent methyl group. Through application of the Eyring equation,[17] these data permitted us to calculate an energy barrier of $\Delta G^{\#} = (15.4 \pm 0.2)$ kcal mol^{-1} for the process, typical for similar conformational restraints.[18] It is reasonable to suppose that this phenomenon occurs in all of the compounds **8**–**17** and **20**–**29**, but it is especially evident for compounds bearing ethoxycarbonyl groups.

Conclusions

The uncatalysed Michael-like addition reactions between supernucleophiles and 1,2-diazabuta-1,3-dienes produce the corresponding 1,4-adducts, which cyclize to pyrazolones and cinnolines under basic conditions. These two heterocyclic derivatives are formed at the same time, and the relative prevalence of each of the two cyclization reaction products depends on the solvent used. The formation of pyrazolones as major products occurs in methanol, whereas the unexpected formation of the cinnoline ring prevails in THF, a more strongly associating solvent, through an intramolecular nucleophilic aromatic substitution involving the displacement of a secondary amino group and represents a new route to cinnoline derivatives.

Experimental Section

General Remarks: NMR spectra were recorded with Varian Gemini 300 or Mercury 400 spectrometers operating at 300 or 400 MHz (for ^1H NMR) or at 75.36 or 100.56 MHz (for ^{13}C NMR), respectively. Signal multiplicities were established by DEPT experiments. Chemical shifts for ^1H NMR spectra in $CDCl_3$ were referenced to TMS; in other cases chemical shifts were referenced to the solvent {$\delta = 77.0$ ppm for ^{13}C in $CDCl_3$, $\delta = 3.31$ and 49.0 ppm for ^1H and ^{13}C, respectively, in CD_3OD, $\delta = 2.0$ and 0.3 ppm for ^1H and ^{13}C, respectively, in CD_3CN, $\delta = 2.49$ and 39.5 ppm for ^1H and ^{13}C, respectively, in [D_6]DMSO; coupling constants (J) in Hertz}. All signals assigned to NH protons disappear after addition of D_2O. NOE and gHSQC experiments were carried out with a Varian Inova 600 spectrometer. ESI-MS spectra were obtained with a WATERS 2Q 4000 instrument. Melting points were determined with a Büchi 535 apparatus in open capillary tubes and are uncorrected. Silica gel plates supported on aluminium were employed for analytical thin layer chromatography (TLC), and silica gel (230–400 mesh) for flash chromatography (FC). IR spectra were recorded on a model 1600 FT-IR Perkin–Elmer spectrophotometer in $CHCl_3$ solution. IR spectra of compounds **8**–**10** and **13**–**15** contain typical signals belonging both to ester (ca. 1830 cm^{-1}) and amido groups (ca. 1692 and 1599 cm^{-1}); NOE experiments showed

the (*E*) configuration for compound **8**. Compounds **11**, **12**, **16**, **17** and **20**–**23** showed typical signals belonging to amido groups. Cinnolines **24**–**29** showed typical signals (ca. 1729, 1609, 1540, 1435, 1380, 1255, 1150 cm^{-1}). Sodium methoxide and solvents used are commercially available materials, starting materials **1** and **2** were synthesized as previously reported,[2a] and **DBD**s **3**,[19] **4**,[20] **5**, **6**,[21] **7**, **18**[22] and **19** were synthesized according to previously reported procedures[23] as (*E*)/(*Z*) mixtures in variable relative ratios, depending on the structures. Their characterization data, if not already reported, are described in the Supporting Information.

Preparation of Semicarbazone Derivatives 8–17

First Procedure: 1,2-Diazabuta-1,3-diene derivative **3** (or **4**–**7**, 0.150 mmol) was added to a solution of **TAB 1** (or **2**, 0.150 mmol in 2 mL of $CHCl_3$) at room temperature with magnetic stirring until disappearance of the red colour of the reaction mixture (from 1 to 8 h). The solution was then concentrated under reduced pressure. The addition of CH_3CN (2–3 mL) to the crude oil caused precipitation of compounds **8**–**17** (>98% pure), which were collected by filtration and analysed by MS and by ^1H and ^{13}C NMR spectroscopy. Further small amounts of compounds **8**–**17** remained in the mother liquor, together, in some cases, with its isomeric product (see later) or, sometimes, with unreacted starting materials. All attempts to separate the reaction products by column chromatography on silica gel (elution: Et_2O/CH_3OH from 0 to 100%, v/v) decreased the yields of adducts, because variable amounts of cyclization product (pyrazolones in 10–20% yields) were obtained after elution with pure methanol under these conditions.

Second Procedure: This procedure exploits the low solubility of products **8**–**17** in CH_3CN and permits the process to be simplified and the recovery of the adducts to be increased. In this case, equimolar amounts of compound **1** and a **DBD** (**3**–**7**) were dissolved in the minimum possible volume of CH_3CN, and the reaction mixture was stirred at room temperature for 1–2 h. Pure compounds **8**–**12** precipitated from the reaction mixture and were recovered by filtration in yields higher than those obtained in the first procedure and in almost pure form. This method cannot be applied to morpholinyl derivatives because of the very low solubility of compound **2** in acetonitrile.

Ethyl 3-[(Aminocarbonyl)hydrazono]-2-(2,4,6-tripiperidin-1-ylphenyl)butanoate (8): Pale yellow solid; 0.059 g (77%); m.p. 121–122 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.25 (t, J = 7.1 Hz, 3 H), 1.40–1.76 (m, 18 H), 1.86 (s, 3 H), 2.50–2.90 (m, 8 H), 3.00–3.18 (m, 4 H), 4.16 (q, J = 7.1 Hz, 1 H), 4.21 (q, J = 7.1 Hz, 1 H), 4.50–4.95 (br. s, 1 H, NH), 5.20 (s, 1 H), 5.45–6.00 (br. s, 1 H, NH), 6.64 (s, 2 H), 7.64 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 14.3 (CH_3), 15.5 (CH_3), 24.2 (CH_2), 24.3 (CH_2), 25.9 (CH_2), 26.3 (CH_2), 50.5 (CH_2), 52.8 (CH), 54.9 (CH_2), 60.2 (CH_2), 107.4 (CH), 121.4, 149.4, 152.5, 154.5, 157.3, 172.1 ppm. MS (ES^+): m/z = 513 $[M + H]^+$. $C_{28}H_{44}N_6O_3$ (512.7): calcd. C 65.60, H 8.65, N 16.39; found C 65.50, H 8.68, N 16.35.

Methyl 3-[(Aminocarbonyl)hydrazono]-2-(2,4,6-tripiperidin-1-ylphenyl)butanoate (9): Pale yellow solid; 0.052 g (70%); m.p. 161–162 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.45–1.65 (m, 12 H), 1.65–1.78 (m, 6 H), 1.90 (s, 3 H), 2.55–2.90 (m, 8 H), 3.10–3.20 (m, 4 H), 3.71 (s, 3 H), 4.20–4.95 (br. s, 1 H, NH), 5.21 (s, 1 H), 5.40–5.90 (br. s, 1 H, NH), 6.64 (s, 2 H), 7.44 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 15.5 (CH_3), 24.2 (CH_2), 24.3 (CH_2), 25.9 (CH_2), 26.3 (CH_2), 50.5 (CH_2), 51.4 (CH), 52.4 (CH_3), 54.7 (CH_2), 107.5 (CH), 121.5, 149.1, 152.6, 154.4, 157.0, 172.6 ppm. MS (ES^+): m/z = 499 $[M + H]^+$. $C_{27}H_{42}N_6O_3$ (498.7): calcd. C 65.03, H 8.49, N 16.85; found C 64.97, H 8.51, N 16.87.

Methyl 3-[(Aminocarbonyl)hydrazono]-2-(2,4,6-tripiperidin-1-ylphenyl)pentanoate (10): Pale green solid; 0.057 g (74%); m.p. 152–153 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.09 (t, J = 7.5 Hz, 3 H), 1.45–1.65 (m, 12 H), 1.65–1.80 (m, 6 H), 2.15–2.30 (dq, J = 7.5 Hz, 1 H), 2.37–2.51 (dq, J = 7.5 Hz, 1 H), 2.51–2.90 (m, 8 H), 3.08–3.18 (m, 4 H), 3.70 (s, 3 H), 4.45–4.80 (br. s, 1 H, NH), 5.29 (s, 1 H), 5.45–5.80 (br. s, 1 H, NH), 6.65 (s, 2 H), 7.72 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 9.6 (CH_3), 22.2 (CH_2), 24.2 (CH_2), 24.3 (CH_2), 25.9 (CH_2), 26.2 (CH_2) 50.0 (CH_3), 50.5 (CH_2), 51.3 (CH), 54.8 (CH_2), 107.7 (CH), 121.9, 152.5, 153.4, 154.3, 157.3, 172.8 ppm. MS (ES^+): m/z = 513 $[M + H]^+$. $C_{28}H_{44}N_6O_3$ (512.7): calcd. C 65.60, H 8.65, N 16.39; found C 65.56, H 8.67, N 16.35.

3-[(Aminocarbonyl)hydrazono]-*N*,*N*-dimethyl-2-(2,4,6-tripiperidin-1-ylphenyl)butanamide (11): White solid; 0.074 g (96%); m.p. 197–207 °C (dec.). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.35–1.62 (m, 12 H), 1.63–1.79 (m, 6 H), 1.84 (s, 3 H) 2.35–2.70 (m, 8 H), 2.81 (s, 3 H), 2.96 (s, 3 H), 3.09–3.18 (m, 4 H), 4.40–4.80 (br. s, 1 H, NH), 5.38 (s, 1 H), 5.62–6.02 (br. s, 1 H, NH), 6.64 (s, 2 H), 7.48 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 15.7 (CH_3), 24.2 (CH_2), 24.3 (CH_2), 25.9 (CH_2), 26.3 (CH_2), 35.6 (CH_3), 37.2 (CH_3), 50.5 (CH_2), 51.6 (CH), 54.9 (CH_2), 107.5 (CH), 122.1, 150.4, 152.4, 154.4, 157.2, 171.5 ppm. MS (ES^+): m/z = 512 $[M + H]^+$. $C_{28}H_{45}N_7O_2$ (511.7): calcd. C 65.72, H 8.86, N 19.16; found C 65.69, H 8.88, N 19.12.

3-[(Anilinocarbonyl)hydrazono]-*N*,*N*-dimethyl-2-(2,4,6-tripiperidin-1-ylphenyl)butanamide (12): White solid; 0.084 g (95%); m.p. 149–150 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.46–1.65 (m, 12 H), 1.68–1.81 (m, 6 H), 1.95 (s, 3 H), 2.40–3.10 (m, 8 H), 2.77 (s, 3 H), 2.98 (s, 3 H), 3.14–3.21 (m, 4 H), 5.38 (s, 1 H), 6.70 (s, 2 H), 6.96–7.03 (m, 1 H), 7.20–7.32 (m, 4 H), 7.51 (br. s, 1 H, NH), 7.88 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 16.3 (CH_3), 24.3 (CH_2), 24.5 (CH_2), 26.0 (CH_2), 26.4 (CH_2), 35.7 (CH_3), 37.3 (CH_3), 50.5 (CH_2), 51.9 (CH), 54.9 (CH_2), 107.7, 118.6, 122.5, 122.7, 128.8, 138.4, 150.6, 152.5, 153.3, 154.2, 171.3 ppm. MS (ES^+): m/z = 588 $[M + H]^+$. $C_{34}H_{49}N_7O_2$ (587.8): calcd. C 69.47, H 8.40, N 16.68; found C 69.50, H 8.43, N 16.64.

Ethyl 3-[(Aminocarbonyl)hydrazono]-2-(2,4,6-trimorpholin-4-ylphenyl)butanoate (13): Pale yellow solid; 0.043 g (55%); m.p. 150–165 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.26 (t, J = 7.2 Hz, 3 H), 1.93 (s, 3 H), 2.74–2.88 (m, 8 H), 3.12–3.20 (m, 4 H), 3.61–3.93 (m, 12 H), 4.15 (q, J = 7.2 Hz, 1 H), 4.21 (q, J = 7.2 Hz, 1 H), 5.10–5.40 (br. s, 1 H, NH), 5.24 (s, 1 H), 5.40–5.70 (br. s, 1 H, NH), 6.66 (s, 2 H), 8.52 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 14.3 (CH_3), 16.2 (CH_3), 48.9 (CH_2), 49.9 (CH_2), 53.5 (CH), 60.5 (CH_2), 66.8 (CH_2), 67.2 (CH_2), 107.1 (CH), 122.4, 148.9, 151.9, 153.2, 157.1, 171.8 ppm. MS (ES^+): m/z = 519 $[M + H]^+$. $C_{25}H_{38}N_6O_6$ (518.6): calcd. C 57.90, H 7.39, N 16.21; found C 57.83, H 7.42, N 16.15.

Methyl 3-[(Aminocarbonyl)hydrazono]-2-(2,4,6-trimorpholin-4-ylphenyl)butanoate (14): Pale yellow solid; 0.063 g (83%); m.p. 166–167 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.95 (s, 3 H), 2.68–2.92 (m, 8 H), 3.11–3.22 (m, 4 H), 3.52–3.80 (m, 8 H), 3.71 (s, 3 H), 3.80–3.92 (m, 4 H), 4.45–4.85 (br. s, 1 H, NH), 5.26 (s, 1 H), 5.30–5.70 (br. s, 1 H, NH), 6.67 (s, 2 H), 7.73 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 16.2 (CH_3), 48.9 (CH_2), 51.6 (CH), 52.3 (CH_3), 53.5 (CH_2), 66.8 (CH_2), 67.1 (CH_2), 107.1 (CH), 122.5, 148.7, 151.9, 153.0, 156.9, 172.3 ppm. MS (ES^+): m/z = 505 $[M + H]^+$. $C_{24}H_{36}N_6O_6$ (504.6): calcd. C 57.13, H 7.19, N 16.66; found C 57.07, H 7.21, N 16.68.

Methyl 3-[(Aminocarbonyl)hydrazono]-2-(2,4,6-trimorpholin-4-ylphenyl)pentanoate (15): White solid; 0.059 g (76%); m.p. 248–

258 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.15 (t, J = 7.7 Hz, 3 H), 2.23–2.37 (m, 1 H), 2.37–2.52 (m, 1 H), 2.62–2.92 (m, 8 H), 3.12–3.22 (m, 4 H), 3.60–3.78 (m, 8 H), 3.70 (s, 3 H), 3.83–3.92 (m, 4 H), 4.45–5.00 (br. s, 1 H, NH), 5.10–5.75 (br. s, 1 H, NH), 5.35 (s, 1 H), 6.68 (s, 2 H), 7.94 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 9.6 (CH_3), 22.6 (CH_2), 49.0 (CH_2), 49.8 (CH_2), 51.5 (CH), 53.6 (CH_3), 66.8 (CH_2), 67.1 (CH_2), 107.3 (CH), 122.8, 151.8, 152.9, 153.0, 157.1, 172.5 ppm. MS (ES^+): m/z = 519 $[M + H]^+$. $C_{25}H_{38}N_6O_6$ (518.6): calcd. C 57.90, H 7.39, N 16.21; found C 57.77, H 7.40, N 16.16.

3-[(Aminocarbonyl)hydrazono]-*N*,*N*-dimethyl-2-(2,4,6-trimorpholin-4-ylphenyl)butanamide (16): White solid; 0.072 g (93%); m.p. 210–217 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.84 (s, 3 H), 2.65–2.92 (m, 8 H), 2.88 (s, 3 H), 2.96 (s, 3 H), 3.16–3.20 (m, 4 H), 3.50–3.80 (m, 8 H), 3.80–3.90 (m, 4 H), 4.45–4.80 (br. s, 1 H, NH), 5.42 (s, 1 H), 5.55–5.90 (br. s, 1 H, NH), 6.65 (s, 2 H), 7.56 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 16.1 (CH_3), 35.7 (CH_3), 37.4 (CH_3), 49.0 (CH_2), 51.8 (CH), 53.7 (CH_2), 66.8 (CH_2), 67.1 (CH_2), 106.8 (CH), 122.5, 149.7, 151.7, 153.2, 157.1, 171.2 ppm. MS (ES^+): m/z = 518 $[M + H]^+$. $C_{25}H_{39}N_7O_5$ (517.6): calcd. C 58.01, H 7.59, N 18.94; found C 57.88, H 7.60, N 18.92.

3-[(Anilinocarbonyl)hydrazono]-*N*,*N*-dimethyl-2-(2,4,6-trimorpholin-4-ylphenyl)butanamide (17): White solid; 0.058 g (65%); m.p. 177–178 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.95 (s, 3 H), 2.62–2.99 (m, 8 H), 2.89 (s, 3 H), 3.02 (s, 3 H), 3.16–3.22 (m, 4 H), 3.45–3.82 (m, 8 H), 3.82–3.98 (m, 4 H), 5.44 (s, 1 H), 6.72 (s, 2 H), 6.98–7.10 (m, 1 H), 7.20–7.28 (m, 4 H), 7.80 (br. s, 1 H, NH), 7.97 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 16.5 (CH_3), 35.7 (CH_3), 37.5 (CH_3), 49.0 (CH_2), 52.0 (CH), 53.6 (CH_2), 67.1 (CH_2), 66.8 (CH_2), 107.1 (CH), 118.6 (CH), 123.1 (CH), 128.9 (CH), 138.1, 150.0, 151.8, 153.1 (2 × sig. overl.), 153.2, 171.0 ppm. MS (ES^+): m/z:594 $[M + H]^+$. $C_{31}H_{43}N_7O_5$ (593.7): calcd. C 62.71, H 7.30, N 16.51; found C 62.69, H 7.32, N 16.47.

Pyrazolone Derivatives 20–23: An equimolar amount of sodium methoxide was added at room temperature to a stirred solution of semicarbazone derivative (**8**–**10** and **13**–**15**, 0.1 mmol) in MeOH (2 mL). The solution became yellow. The mixture was stirred for 24–36 h, until disappearance of starting semicarbazone. The solvent was removed under reduced pressure, and the crude material was purified by column chromatography (elution with diethyl ether/MeOH mixtures) to give pure pyrazolone derivatives **20**–**23**.

3-Methyl-5-oxo-4-(2,4,6-tripiperidin-1-ylphenyl)-2,5-dihydro-1*H*-pyrazole-1-carboxamide (20): 0.036 g (77% from **9**). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.40–1.80 (m, 18 H), 2.27 (s, 3 H), 2.60–3.10 (m, 8 H), 3.10–3.20 (m, 4 H), 4.35–4.96 (br. s, 1 H, NH_2), 5.10–5.55 (br. s, 1 H, NH_2), 6.47 (s, 2 H), 6.52 (br. s, 1 H, NH) ppm. ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 1.65–1.97 (m, 18 H), 2.41 (s, 3 H), 2.90–3.01 (m, 8 H), 3.31–3.37 (m, 4 H), 6.72 (s, 2 H) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 13.4 (CH_3), 24.2 (CH_2), 24.3 (CH_2), 26.0 (CH_2), 26.1 (CH_2), 50.7 (CH_2), 53.5 (CH_2), 101.4, 103.2 (CH), 103.8, 113.0, 139.2, 152.1, 153.1, 158.9 ppm. MS (ES^+): m/z = 467 $[M + H]^+$. $C_{26}H_{38}N_6O_2$ (466.6): calcd. C 66.92, H 8.21, N 18.01; found C 66.99, H 8.18, N 18.05.

3-Ethyl-5-oxo-4-(2,4,6-tripiperidin-1-ylphenyl)-2,5-dihydro-1*H*-pyrazole-1-carboxamide (21): 0.044 g (92%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.06 (t, J = 7.6 Hz, 3 H), 1.35–1.85 (m, 18 H), 2.60–3.10(m, 8 H), 2.80 (q, J = 7.6 Hz, 2 H), 3.10–3.20 (m, 4 H), 4.45–5.00 (br. s, 2 H, NH_2), 6.45 (s, 2 H), 6.48 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 12.2 (CH_3), 21.1 (CH_2), 24.2 (CH_2), 24.3 (CH_2), 26.0 (CH_2), 26.2 (CH_2), 50.7 (CH_2), 53.4 (CH_2), 100.4, 103.1 (CH), 103.8, 113.2, 144.2, 152.1, 153.0, 158.9 ppm. MS (ES^+): m/z = 481 $[M + H]^+$. $C_{27}H_{40}N_6O_2$ (480.6): calcd. C 67.47, H 8.39, N 17.48; found C 67.35, H 8.41, N 17.44.

3-Methyl-5-oxo-4-(2,4,6-trimorpholin-4-ylphenyl)-2,5-dihydro-1*H*-pyrazole-1-carboxamide (22): 0.019 g (40% from **13**). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.85 (s, 3 H), 2.40–3.05 (m, 8 H), 3.10–3.30 (m, 4 H), 3.55–3.80 (m, 8 H), 3.80–4.00 (m, 4 H), 4.65–5.15 (br. s, 2 H, NH_2), 6.42 (br. s, 1 H, NH), 6.43 (s, 2 H) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 13.2 (CH_3), 49.2 (CH_2), 52.3 (CH_2), 66.85 (CH_2), 66.92 (CH_2), 101.0, 102.2 (CH), 102.9, 112.7, 138.8, 151.7, 152.2, 158.6 ppm. MS (ES^+): m/z = 473 $[M + H]^+$. $C_{23}H_{32}N_6O_5$ (472.5): calcd. C 58.46, H 6.83, N 17.78; found C 58.24, H 6.86, N 17.72.

3-Ethyl-5-oxo-4-(2,4,6-trimorpholin-4-ylphenyl)-2,5-dihydro-1*H*-pyrazole-1-carboxamide (23): 0.027 g (55%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.11 (t, J = 7.5 Hz, 3 H), 2.37–3.46 (m, 14 H), 3.55–3.80 (m, 8 H), 3.82–4.00 (m, 4 H), 4.55–5.00 (br. s, 2 H, NH_2), 6.43 (s, 2 H), 6.69 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 12.3 (CH_3), 21.0 (CH_2), 46.7(CH_2), 49.2 (CH_2), 52.2 (CH_2), 66.8 (CH_2), 66.9 (CH_2), 67.4 (CH_2), 99.9, 102.1 (CH), 103.1, 112.9, 143.8, 151.7, 152.1, 158.5 ppm. MS (ES^+): m/z = 487 $[M + H]^+$. $C_{24}H_{34}N_6O_5$ (486.6): calcd. C 59.24, H 7.04, N 17.27; found C 59.30, H 7.06, N 17.21.

Cinnoline Derivatives 24–29: Sodium methoxide (0.2 mmol) was added to a stirred solution of a semicarbazone (**8**–**10** or **13**–**15**, 0.1 mmol) in THF (2 mL). A red colour developed. The reaction mixture was stirred until the disappearance of the red colour, and the THF was then removed under reduced pressure. The crude material was purified by FC on silica gel (eluents: light petroleum/diethyl ether mixtures), and the pure cinnoline (**24**–**29**) was obtained.

Ethyl 3-Methyl-5,7-dipiperidin-1-ylcinnoline-4-carboxylate (24): Orange oil; 0.0275 g (72%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.40 (t, J = 7.2 Hz, 3 H), 1.44–1.88 (m, 12 H), 2.30–3.05 (m, 2 H), 2.80 (s, 3 H), 2.93–3.02 (m, 2 H), 3.20–3.40 (m, 4 H), 4.21–4.34 (br m, 1 H), 4.55–4.77 (br m, 1 H), 7.36 (d, J = 2.5 Hz, 1 H), 7.49 (d, J = 2.5 Hz, 1 H) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 14.0 (CH_3), 19.3 (CH_3), 23.7 (CH_2), 24.2 (CH_2), 24.9 (br. s, CH_2), 25.5 (CH_2), 26.0 (br. s, CH_2), 49.9 (CH_2), 53.5 (br. s, CH_2), 57.5 (br. s, CH_2), 61.5 (CH_2), 106.5 (CH), 115.2, 118.5, 124.0, 147.5, 150.3, 152.2, 152.5, 168.2 ppm. MS (ES^+): m/z = 383 $[M + H]^+$. $C_{22}H_{30}N_4O_2$ (382.5): calcd. C 69.08, H 7.91, N 14.65; found C 69.11, H 7.93, N 14.62.

Methyl 3-Methyl-5,7-dipiperidin-1-ylcinnoline-4-carboxylate (25): Orange oil; 0.0331 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.40–2.10 (m, 12 H), 2.20–3.10 (m, 4 H), 2.78 (s, 3 H), 3.30–3.42 (m, 4 H), 4.01 (s, 3 H), 7.36 (d, J = 2.4 Hz, 1 H), 7.50 (d, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 19.3 (CH_3), 23.7 (CH_2), 24.2 (CH_2), 24.9 (br. s, CH_2), 25.5 (CH_2), 26.0 (br. s, CH_2), 49.8 (CH_2), 52.5 (CH_3), 53.6 (br. s, CH_2), 56.7 (br. s, CH_2), 106.4 (CH), 115.2, 118.5 (CH), 123.9, 147.4, 150.2, 152.1, 152.5, 168.7 ppm. MS (ES^+): m/z = 369 $[M + H]^+$. $C_{21}H_{28}N_4O_2$ (368.5): calcd. C 68.45, H 7.66, N 15.21; found C 68.49, H 7.64, N 15.18.

Methyl 3-Ethyl-5,7-dipiperidin-1-ylcinnoline-4-carboxylate (26): Orange oil; 0.0176 g (46%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.21 (t, J = 7.6 Hz, 3 H), 1.50–2.45 (m, 12 H), 2.70–3.22 (m, 4 H), 3.05 (q, J = 7.6 Hz, 2 H), 3.32–3.42 (m, 4 H), 4.00 (s, 3 H), 7.36 (d, J = 2.4 Hz, 1 H), 7.51 (d, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 14.7 (CH_3), 23.7 (CH_2), 24.2 (CH_2), 24.9 (br. s, CH_2), 25.5 (CH_2), 26.0 (br. s, CH_2),

27.0 (CH_2), 49.9 (CH_2), 52.3 (CH_3), 53.7 (br. s, CH_2), 56.8 (br. s, CH_2), 106.6 (CH), 115.2, 118.5 (CH), 123.2, 150.4, 152.1, 152.4, 152.6, 168.6 ppm. MS (ES^+): *m/z* = 383 $[M + H]^+$. $C_{22}H_{30}N_4O_2$ (382.5): calcd. C 69.08, H 7.91, N 14.65; found C 69.05, H 7.92, N 14.67.

Ethyl 3-Methyl-5,7-dimorpholin-4-ylcinnoline-4-carboxylate (27): Yellow solid; 0.0212 g (55%); m.p. 204–214 °C (dec.). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.41 (t, *J* = 7.6 Hz, 3 H), 2.59–3.34 (m, 4 H), 2.83 (s, 3 H), 3.23–3.43 (m, 4 H), 3.55–3.90 (m, 4 H), 3.90–3.98 (m, 4 H), 4.38 (br. m, 1 H, CH_2), 4.75 (br. m, 1 H, CH_2), 7.37 (d, *J* = 2.5 Hz, 1 H), 7.57 (d, *J* = 2.5 Hz, 1 H) ppm. ^1H NMR (400 MHz, $[D_6]$DMSO, 115 °C): δ = 1.36 (t, *J* = 7.0 Hz, 3 H), 2.71 (s, 3 H), 2.77–2.99 (m, 4 H), 3.38–3.46 (m, 4 H), 3.62–3.80 (m, 4 H), 3.79–3.87 (m, 4 H), 4.50 (q, *J* = 7.0 Hz, 2 H), 7.45 (d, *J* = 2.5 Hz, 1 H), 7.61 (d, *J* = 2.5 Hz, 1 H) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 14.1 (CH_3), 19.4 (CH_3), 48.7 (CH_2), 52.3 (br. s, CH_2), 55.4 (br. s, CH_2), 61.7 (CH_2), 66.6 (CH_2), 107.4 (CH), 115.2, 117.6 (CH), 123.8, 148.0, 149.0, 151.8 (2 signals overlapped), 168.3 ppm. MS (ES^+): *m/z* = 387 $[M + H]^+$. $C_{20}H_{26}N_4O_4$ (386.4): calcd. C 62.16, H 6.78, N 14.50; found C 62.21, H 6.80, N 14.53.

Methyl 3-Methyl-5,7-dimorpholin-4-ylcinnoline-4-carboxylate (28): Yellow solid; 0.0153 g (41%); m.p. 201–209 °C (dec.). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.60–3.30 (m, 4 H), 2.81 (s, 3 H), 3.30–3.45 (m, 4 H), 3.45–4.00 (m, 4 H), 3.90–3.96 (m, 4 H), 4.06 (s, 3 H), 7.37 (d, *J* = 2.5 Hz, 1 H), 7.57 (d, *J* = 2.5 Hz, 1 H) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 19.5 (CH_3), 48.7 (CH_2), 52.5 (br. s, CH_2), 52.6 (CH_3), 55.3 (br. s, CH_2), 66.6 (CH_2), 107.3 (CH), 115.1, 117.6 (CH), 123.6, 148.0, 148.9, 151.76, 151.84, 168.8 ppm. MS (ES^+): *m/z* = 373 $[M + H]^+$. HRMS calcd. for $C_{19}H_{24}N_4O_4$ 372.17976; found 372.1799. $C_{19}H_{24}N_4O_4$ (372.4): calcd. C 61.28, H 6.50, N 15.04; found C 61.25, H 6.51, N 15.00.

Methyl 3-Ethyl-5,7-dimorpholin-4-ylcinnoline-4-carboxylate (29): Yellow solid; 0.0178 g (46%); m.p. 214–224 °C (dec.). ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.43 (t, *J* = 7.6 Hz, 3 H), 2.58–3.35 (m, 4 H), 3.06 (q, *J* = 7.6 Hz, 2 H), 3.32–3.41 (m, 4 H), 3.62–4.00 (m, 4 H), 3.90–3.96 (m, 4 H), 4.05 (s, 3 H), 7.37 (d, *J* = 2.5 Hz, 1 H), 7.58 (d, *J* = 2.5 Hz, 1 H) ppm. ^{13}C NMR (100.56 MHz, $CDCl_3$, 25 °C): δ = 14.7 (CH_3), 27.1 (CH_2), 48.7(CH_2), 52.4 (br. s, CH_2), 52.5 (CH_3), 55.4 (br. s, CH_2), 66.6 (CH_2), 107.5 (CH), 115.1, 117.5 (CH), 123.0, 149.1, 151.7, 151.9, 152.9, 168.7 ppm. MS (ES^+): *m/z* = 387 $[M + H]^+$. $C_{20}H_{26}N_4O_4$ (386.4): calcd. C 62.16, H 6.78, N 14.50; found C 62.19, H 6.79, N 14.48.

Study on the Formation of Semicarbazone Derivatives 8 and 13: Compound **3** (0.030 mmol), dissolved in CD_3CN (0.5 mL), was added at –30 °C to an equimolar amount of **1** (or **2**, in 0.5 mL of CD_3CN) directly in an NMR tube. The ^1H NMR spectrum of the obtained solution showed the disappearance of the signals of the starting materials and the appearance of new signals, attributable to compound **8** (or **13**). The reaction was monitored over 2 h. The same reaction was also carried out in CD_3CN at 25 °C, in $CDCl_3$ at –30 °C and at 25 °C and in CD_2Cl_2 at –70 °C. In all cases no evidence of formation of Wheland complexes was obtained, but after about 1 h new stable signals, ascribed to an isomeric form of **8** (or **13**), appeared (see following paragraph).

On the Isomerism of Semicarbazone Derivatives 8–10 and 13–15: Solutions containing the pure compounds **8**–**10** and **13**–**15** in $CDCl_3$ at 25 °C were monitored by ^1H NMR spectroscopy. In each case the related ^1H NMR spectrum showed the appearance, after about 30 min, of new signals very similar to those of the starting semicarbazone. These signals might be attributable to a tautomeric form. After at least 2 d, the ratio between the two forms was about 80:20 and remained stable with time. A mixture containing compound **8** and its isomeric form was dissolved in CD_3CN and monitored by VT ^1H NMR experiments from –30 °C to +75 °C. Cooling to –30 °C caused partial precipitation of starting materials, but the spectrum showed an unmodified relative ratio of the two compounds. Gradual heating caused redissolution of the solid, but the relative product ratio remained unchanged. Because all attempts to separate isomeric forms from the main compounds **8**–**10** and **13**–**15** by FC failed (in addition, during FC the formation of cyclization products occurred), we report here only the ^1H NMR signals of minor isomers present in the spectra of the mixtures.

Isomer of Compound 8: ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.28 (t, *J* = 7.1 Hz, 3 H), 1.40–1.76 (m, 18 H), 2.40 (s, 3 H), 2.50–2.90 (m, 8 H), 3.00–3.24 (m, 4 H), 4.33 (q, *J* = 7.1 Hz, 1 H), 4.41 (q, *J* = 7.1 Hz, 1 H), 5.15 (s, 1 H), 6.75 (s, 2 H), 8.35 (br. s, 1 H, exch.) 8.36 (br. s, 2 H, exch.) ppm.

Isomer of Compound 9: ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): 1.50–1.65 (m, 12 H), 1.65–1.80 (m, 6 H), 2.18 (s, 3 H), 2.55–2.90 (m, 8 H), 3.05–3.20 (m, 4 H), 3.72 (s, 3 H), 5.11 (s, 1 H), 6.67 (s, 2 H), 8.50 (br. s, 1 H, exch.) 8.71 (br. s, 2 H, exch.) ppm.

Isomer of Compound 10: ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.13 (t, *J* = 7.5 Hz, 3 H), 1.40–1.90 (m, 18 H), 2.15–2.30 (dq, *J* = 7.5 Hz, 1 H), 2.37–2.51 (dq, *J* = 7.5 Hz, 1 H), 2.58–3.08 (m, 8 H), 3.08–3.28 (m, 4 H), 3.70 (s, 3 H), 5.13 (s, 1 H), 6.67 (s, 2 H), 8.50 (br. s, 1 H, exch.), 8.95 (br. s, 2 H, exch.) ppm.

Isomer of Compound 13: ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.28 (t, *J* = 7.2 Hz, 3 H), 2.40 (s, 3 H), 2.45–3.20 (m, 8 H), 3.12–3.20 (m, 4 H), 3.61–3.93 (m, 12 H), 4.12 (q, *J* = 7.1 Hz, 1 H), 4.26 (q, *J* = 7.1 Hz, 1 H), 5.16 (s, 1 H), 6.70 (s, 2 H), 8.37 (br. s, 1 H, exch.) ppm.

Isomer of Compound 14: ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.17 (s, 3 H), 2.68–2.92 (m, 8 H), 3.11–3.22 (m, 4 H), 3.62–3.80 (m, 8 H), 3.73 (s, 3 H), 3.80–3.98 (m, 4 H), 5.15 (s, 1 H), 6.70 (s, 2 H), 8.55 (br. s, 1 H, exch.) ppm.

Isomer of Compound 15: ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.09 (t, *J* = 7.7 Hz, 3 H), 2.24–2.40 (m, 1 H), 2.41–2.61 (m, 1 H), 2.62–3.05 (m, 8 H), 3.12–3.22 (m, 4 H), 3.56–3.78 (m, 8 H), 3.72 (s, 3 H), 3.83–3.92 (m, 4 H), 5.21 (s, 1 H), 6.70 (s, 2 H), 8.77 (br. s, 1 H, exch.), 8.99 (br. s, 2 H, exch.) ppm.

Supporting Information (see footnote on the first page of this article): Characterization data for compounds **5**–**17** and **20**–**29** and copies of ^1H and ^{13}C NMR spectra of new compounds **8**–**17**, and **20**–**29**.

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